every scheduled visit (8 weeks) until disease progression. Cobas EGFR Mutation Test v1 and v2 (Roche, USA) was used to detect 42 mutations at EGFR gene in exons 18 to 21, including T790M mutation. Radiological assessment was performed in accordance with RECIST 1.1 criteria. **Result:** Twenty-seven patients were treated with osimertinib from October 2015 until December 2018. At the beginning of osimertinib treatment only 17/27 (63%) patients had detectable T790M mutation in plasma, but almost all patients 26/27 (96%) had detectable plasma EGFR activating mutations (AM). During osimertinib treatment T790M mutation was cleared from plasma in all 17 patients regardless of response to treatment. On the contrary, only 12/26 (45%) patients had AM plasma clearance. Only 3 of them had had progress at median follow up of 17.5 months, what demonstrates significantly longer progression-free survival (PFS) of patients with AM plasma clearance compared to patients without AM clearance (HR 0.19; 95% CI 0.05 − 0.70, p = 0.01) (*Figure 1*). Of the 14 patients that progressed during the observation period all had AM reapperance in cfDNA at the time on progression, while T790M only recurred in one.

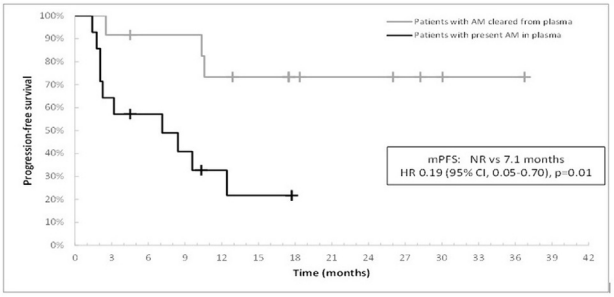

Figure 1: Progression free survival in patients receiving osimertinib for advanced EGFRmu T790M positive NSCLC. **Grey line** - patients with negativisation of EGFR activating mutations, **black line** - patients without negativisation of EGFR activating mutations when receiving osimertinib, NR denotes not reached.

Conclusion: Clearance of EGFR AM in plasma during osimertinib treatment is associated with longer PFS, while clearance of T790M has no impact on survival in our small group of patients. Dynamic changes in EGFR AM might be a useful marker of outcome in patients treated with osimertinib, but further studies are needed. **Keywords:** EGFR mutations, osimertinib, NSCLC

P1.14-15
Lorlatinib in ALK- or ROS1-Positive Non-Small Cell Lung Cancer Patients: Experience from an Early Access Program in Turkey

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Background: Lorlatinib, a third generation ALK and ROS1 inhibitor, is indicated for the treatment of patients with *ALK+* metastatic NSCLC whose disease has progressed on crizotinib and at least one second-generation ALK inhibitor. The aim of this study is to evaluate the efficacy and safety of lorlatinib in an Expanded Access Program (EAP) in Turkey. **Method:** The EAP was open-label, multicenter, and single-arm. Patients were eligible to receive lorlatinib (100 mg p.o/day) if they had advanced stage *ALK-* or *ROS1*-positive NSCLC and had progressed on crizotinib and/or second generation ALK inhibitors such as ceritinib or alectinib. The primary endpoint was PFS with lorlatinib. Secondary endpoints were objective response rate, overall survival, and safety. **Result:** Between February 2017 and December 2018, a total of 91 patients were admitted to the EAP at 27 oncology centers in Turkey. Eleven patients died before receiving the drug. Four patients were excluded from the EAP because of lost of the follow-up. Of the 76 patients who received drug, 13 were excluded from the analysis due to inability to access patient information. Six of these 13 patients were on lorlatinib treatment at the time of data collection. The median age of patients was 53.5 (17-84) years. Of 63 evaluable patients, 55 (87.3%) had *ALK+* NSCLC and 8 (12.7%) had *ROS1+* NSCLC. All patients had adenocarcinoma histology, and 54% (n=34) had brain metastasis before lorlatinib treatment. Twenty-one patients received lorlatinib as third-line treatment (mostly after chemotherapy and crizotinib). Median follow-up was 9.1 months. Five patients died before the first evaluation of response. In patients who received at least 1 dose of lorlatinib, median PFS was 12.6 months, and 1-year PFS rate was 53%. In *ALK+* patients, median PFS was 14.7 months and 1-year PFS rate was 55%. In *ROS1+* patients, median PFS was 9.1 months and 1-year PFS rate was 47%. In patients who received only crizotinib prior to lorlatinib, median PFS was 14.8 months and 1-year PFS rate was 59%. In patients who received ≥2 ALK inhibitors prior to lorlatinib, median PFS was 5.1 months and 1-year PFS rate was 27%. One-year OS rate was 65%. In response-evaluable patients (n=55), the ORR and DCR were 68.6% and 87.0% all patients. However, ORR and DCR were 69.6% and 87.0% for *ALK+* and 62.5% and 87.5% for *ROS1+* patients. Of response-evaluable 55 patients, the frequency of brain metastasis before lorlatinib was 54.5% (n=30). In only 7 patients (12.7%), brain metastasis developed under lorlatinib treatment. CNS control rate with lorlatinib was 87.3%. Dose reduction occurred in 9 patients (14.3%). Reasons for discontinuation of treatment were disease progression (n=17,

26.8%), adverse events (n=2, 3.2%), death (n=13, 20.6%), and unknown reasons (n=13, 20.6%). **Conclusion:** In this EAP, lorlatinib showed systemic activity in patients with advanced *ALK*+ or *ROS1*+ NSCLC, regardless of CNS metastases and previous TKI treatment. **Keywords:** ALK positive; ROS1 positive; Lorlatinib; Advanced stage lung cancer

P1.14-16
Resolving Resistance to Osimertinib by Combining Apatinib and Osimertinib in EGFR-Mutant NSCLC Patients

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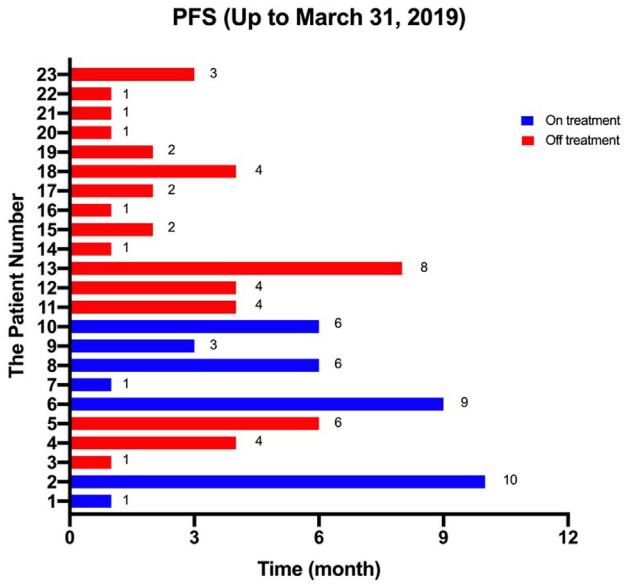
Background: There are currently limited treatment options after osimertinib resistance. Resistance to epidermal growth factor receptor (EGFR) inhibitors is frequently associated with enhanced vascular endothelial growth factor(VEGF) levels. Dual inhibition of the VEGF receptor(VEGFR) and EGFR signaling pathways has the potential to overcome osimertinib resistance. Apatinib is an oral tyrosine kinase inhibitor (TKI) against VEGFR-2. This study was conducted to evaluate the efficacy of Apatinib plus osimertinib after osimertinib resistance in EGFR-mutant NSCLC patients. **Method:** The study was expected to enroll 30 EGFR-mutant NSCLC patients resistant to osimertinib. Patients received oral apatinib 250mg QD plus osimertinib 80mg qd. Efficacy evaluation was conducted after first month, then every two months once again. The primary endpoint was progression free survival (PFS). **Result:** From March 01, 2018 to February 28, 2019, 23 patients were enrolled. The overall response rate (ORR) and disease control rate(DCR)of apatinib plus osimertinib after osimertinib resistance was 8.7%(2/23) and 73.9%(17/23), respectively. Until the last follow-up (March 31,2019), 17 patients (73.9%,17/23) showed disease progression, the other 6 patients (26.1%,6/23) still received combination therapy, as shown in figure 1. The median PFS was 4.0 months (95% CI 2.4-5.5).Six patients had received at least six-month combination therapy, four of whom were still on treatment. The most common adverse event was hypertension, diarrhea, rash and hand-foot syndrome. What calls for special attention is that one patient achieved partial response, however, stopped the combination therapy due to seriously decreased left ventricular ejection fraction.



Conclusion: Apatinib plus osimertinib might be a choice after osimertinib resistance. For further investigation, large sample and additional clinical trials are warranted. **Keywords:** combination therapy, osimertinib resistance, apatinib

P1.14-17
Genomic Evolution During TKI Treatment in Non-Small Cell Lung Cancer Patients With or Without Acquired T790M Mutation

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Background: *EGFR*-mutant non-small-cell lung cancer (NSCLC) patients inevitably develop drug resistance when treated with EGFR tyrosine kinase inhibitors (TKIs). Clonal and clinical analyses of genetic alterations at baseline and progressive disease (PD), as well as differences between acquired T790M and T790M-negative patients in drug-resistant mechanisms, have not been systematically studied. **Method:** We performed targeted sequencing of pre-treatment and PD tumor samples from 54 *EGFR*-mutant NSCLC patients. Ten additional patients were sequenced using whole exome sequencing to infer the clonal evolution patterns. **Result:** We observed new co-occurring alterations and pathways limiting *EGFR*-inhibitor response, including 9p34.3/19p13.3 (*NOTCH1/STK11)* co-deletion and TGF-beta pathway alterations. Besides acquired T790M mutation, chromosomal instability (CIN) related genes including *AURKA* and *TP53* alterations were the most frequently acquired events. CIN significantly increased with TKI treatment in T790M-negative patients. Transcriptional regulators including *HNF1A*, *ATRX* and *NKX2-1* acquired alterations were enriched in T790M-positive patients, and diverse oncogenic pathway alterations were more common in T790M-negative patients. T790M-positive patients had improved PFS compared to T790M-negative patients. We further identified subgroups within T790M-positive or T790M-negative patients with distinct PFS. Clonal evolution analysis indicated progression of T790M-positive patients depends on competition between T790M and non-T790M resistant subclones. **Conclusion:** Our study is the first attempt to identify co-occurring copy number events to stratify patients resistant to TKI treatment. Besides acquired T790M mutation, chromosomal instability (CIN) related genes were identified as the most frequently acquired events. Clonal evolution analysis indicated indicate that higher competitive advantage of T790M was associated with improved PFS. **Keywords:** resistant mechanism, Clonal evolution, EGFR mutant NSCLC

P1.14-18
ALK Inhibitor Sequencing and Outcomes Among ALK-Positive (ALK+) NSCLC Patients in the US Community Oncology Setting

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